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Efficacy and safety of Vonoprazan-based treatment of *Helicobacter pylori* infection: a systematic review and network meta-analysis

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Abstract

Objective The aim of this study was to evaluate the effectiveness and safety of the nine most widely studied Vonoprazan (VPZ)-based treatment regimens along with traditional Proton pump inhibitor (PPI)-based treatment regimens in eradicating *Helicobacter pylori* (*H. pylori*) infection.

Design Through searching PubMed, Embase, Cochrane Library, Web of Science, we exclusively included randomized controlled trials (RCTs) to investigate the efficacy of VPZ-based and PPI-based therapies for *H. pylori* infection. The included studies were evaluated for methodological quality using the Cochrane bias risk assessment tool, and the data analysis software was used to analyze the data accordingly.

Results The RCTs were collected from the earliest available date up to August 2023. Twenty-one RCTs were included, with a total sample size of 5481. The results of the network meta-analysis showed that the eradication rate of the VPZ-based quadruple 14-day (VPZ-Q14) treatment regimen in Intention-to-treat (ITT) analysis was the highest (SUCRA: 0.874); The eradication rate of the VPZ-based quadruple 10-day (VPZ-Q10) treatment plan in Per-protocol (PP) analysis was the highest (SUCRA: 0.849). All regimens were well tolerated without significant differences. According to the probability ranking of safety, high-dose VPZ-based dual 14-day therapy (H-VPZ-D14) ranked first in SUCRA, reaching 0.952. This indicates that H-VPZ-D14 treatment is the safest with a relatively low incidence of adverse effect. Therefore, VPZ-based therapies not only have a higher eradication rate, but also possess satisfactory safety.

Conclusion Compared with traditional PPI-based therapies, VPZ-based therapies have shown superior eradication effects. Based on the Ranking Plot of the Network, the VPZ-Q14 or VPZ-Q10 treatment regimen for *H. pylori* has a higher eradication rate and acceptable differences compared to other treatment regimens. In addition, for regions with high antibiotic resistance rates, we recommend a 14-day quadruple therapy with bismuth based on VPZ.

Keywords *H. Pylori*, PPI-based, VPZ-based, Network meta-analysis

Introduction

Helicobacter pylori (*H. pylori*) is considered one of the most common bacterial pathogens in humans. Currently, *H. pylori* infection remains a major cause of morbidity and mortality worldwide. Overall, the prevalence of *H. pylori* infection, especially in children and younger adults, has been gradually decreasing in developed countries and in countries that have undergone rapid economic development [1]. However, in developing countries and some

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industrialized countries, the infection rate remains very high. *H. pylori* may infect about half of the world's population [2]. Epidemiological studies have shown that there are significant regional differences in the prevalence of *H. pylori* worldwide, particularly in relation to socio-economic development levels and health conditions. *H. pylori* infection is prevalent in developing countries, with infection rates reaching 80% or higher among African adults [3]. Next are Latin America (63.4%) and Asia (54.7%) [4]. Cho et al.'s research on East Asia reveals that the aggregate prevalence of *H. pylori* in the Chinese Mainland is 44.2%, with an estimated 589 million people infected. In Japan, a country that actively screens for *H. pylori*, the incidence rate is reported as 37.6-43.2%, while in South Korea it is 51.0% [5]. Moreover, the recurrence rate of *H. pylori* in developing countries is much higher than that in developed countries [6]. This situation puts greater pressure on resource-scarce areas to eradicate *H. pylori* infection and prevent recurrence. Moreover, *H. pylori* not only has a high infection rate but also seriously endangers human health. It causes a variety of gastric diseases, including several upper gastrointestinal diseases such as chronic gastritis, peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoma (MALT) [7], Furthermore, it causes extragastric diseases, serving as an important trigger for colorectal cancer, in addition to skin (including rosacea, chronic urticaria, atopic dermatitis, etc.), liver diseases (cholangiocarcinoma), hematological diseases (unexplained iron deficiency anemia and vitamin B12 deficiency), neurological diseases (Alzheimer's disease, Parkinson's disease, multiple sclerosis, and Guillain Barre syndrome), and growth disorders in children [8–11]. Recognized as the foremost risk factor for gastric cancer, *H. pylori* has been categorized as an IARC Class I carcinogen by the International Agency for Research on Cancer [12]. In 2015, the gastroenterology community officially recognized *H. pylori* gastritis as an infectious disease and recommended that whenever *H. pylori* is diagnosed with infection, it be eradicated [13].

The universally applicable principles of antibiotic treatment for *H. pylori* have been established. The first eradication principle generally adopts empirical therapy. Currently, most regions around the world still use Proton pump inhibitor (PPI)-based treatment plans. PPI is a prodrug that is activated by acid [14]. Its main function is to significantly and persistently reduce the production of gastric acid by inhibiting the proton pump (H^+/K^+-ATPase) system on the surface of parietal cells [15]. To achieve the best therapeutic effect and ensure sufficient acid suppression, optimal treatment involves selecting an effective combination of antibiotics, while also ensuring adequate treatment duration and compliance. In many parts of the world, the most commonly used first-line treatment for *H. pylori* infection is triple therapy (PPI-AC) based on PPIs, amoxicillin, and clarithromycin. However, due to increasing resistance rates of *H. pylori* to different antibiotics, especially clarithromycin, the incidence of treatment failure is rising. These are the main reasons for treatment failure. Secondary causes of eradication failure are primarily related to the virulence of *H. pylori* strains, high bacterial load, high gastric acidity, and poor compliance. Currently, the eradication rate of *H. pylori* using standard triple therapy has decreased to less than 80% globally [16]. Another important option for first-line treatment through research on eradication plans in multiple regions around the world is Bismuth-based Quadruple Therapy (PPI-BTM), consisting of PPI, bismuth, tetracycline, and metronidazole. Additionally, recommended first-line treatment options include non-bismuth quadruple therapy, such as concomitant therapy, sequential therapy, or 7-day standard triple therapy after clarithromycin resistance testing, and high-dose dual therapy. To achieve a higher eradication rate than empirical treatment, the best treatment plan should be chosen based on antibiotic resistance before initiating treatment. However, due to the slow growth and strict cultivation conditions of *H. pylori*, it is difficult to apply culture-based results to clinical practice. Therefore, antibiotic resistance testing is recommended for use in difficult-to-treat or second-line treatment situations. In order to improve treatment effectiveness, new treatment plans are being tested, including adjuvant therapies with probiotics and traditional Chinese medicine, and the utilization of nanotechnology. However, these new technologies have not yet matured, and commonly used preventive vaccines have not been developed. Based on some characteristics of PPIs in traditional therapies, such as their short half-life, insufficient acid suppression, and pharmacokinetic differences between different races, PPIs may not be an ideal treatment option worldwide [17]. With the dynamic changes in the epidemiology of *H. pylori* and the escalating challenge of antibiotic resistance, a new method for effective management is imperative.

Research on traditional treatment regimens has shown that antibiotics have nearly reached their efficacy threshold in eradicating *H. pylori*. Therefore, acid blockers, when used in combination with antibiotics, are gaining increasing attention. Vonoprazan (VPZ) is a potassium-competitive acid blocker. Its mechanism of action is that VPZ inhibits H^+, K^+-adenosine triphosphatase (ATPase) by reversibly competing with potassium ions, thereby inhibiting gastric acid secretion [18]. An advantage of VPZ over PPIs is its independence from acid activation and its ability to provide a relatively fast and sustained acid-inhibiting effect, which is not influenced by diet or genetic polymorphism [19]. VPZ raises the pH level in

the stomach, thereby enhancing the sensitivity of bacteria to antibiotics, leading to an increased eradication rate. In 2014, VPZ was employed in Japan for the treatment of *H. pylori* infection [20]. Currently, it is considered a first-line medication for eradicating *H. pylori* in Japan. Commonly reported treatment regimens involving VPZ include the VPZ triple 7/14-day regimen, high- or low-dose VPZ dual 7/14-day regimen, and the VPZ quadruple 10/14 regimen. Multiple studies have demonstrated that VPZ-based treatment for eradicating *H. pylori* is either superior or non-inferior to treatment based on traditional PPIs [21–23]. Additionally, the VPZ-based regimen for *H. pylori* proved to be effective and safe for adolescents, similar to its efficacy in adults, for both primary and secondary eradication therapies [24]. Currently, research on VPZ-based treatment regimens is increasingly comprehensive. Our study aims to comprehensively compare various VPZ-based treatment regimens, offer more informed recommendations for clinical practitioners in selecting treatment plans, and serve as a reference for regions that have not yet adopted VPZ for eradicating *H. pylori*.

Network meta-analysis (NMA) is a recent evidence-based technique with significant advantages. These include the capability to compare multiple interventions in a single coherent analysis, provide direct estimates of the relative effects of all available interventions, infer indirect effect estimates for interventions not directly compared, and generate rankings of the available treatment options [25]. This study utilized NMA to analyze and compare the efficacy and safety of nine VPZ-based dual, triple, and quadruple treatment regimens (which included variations in treatment durations and doses), as well as three traditional PPI-based treatment regimens, for patients with *H. pylori* infection. The aim of this study is to offer evidence-based recommendations for patients and clinical physicians.

Materials and methods

We prospectively registered this meta-analysis on PROSPERO (CRD42023495291). The registration includes details on the research purpose, methods, data analysis plan, and other pertinent information.

Search strategy

The researchers in this paper searched four electronic databases (PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science) from their inception until August 30, 2023. Additionally, 14 new articles were identified through manual searches. The search strategy was structured according to the PICOS tool: (P) Population: individuals with *H. pylori* infection. Specifically, the research subjects encompass patients diagnosed with *H. pylori* positivity, irrespective of gender, nationality, race, or severity of the condition, and confirmed through one or more diagnostic tests. Diagnostic methods included: (1) invasive examinations such as endoscopy, histological examination, and rapid urease test (RUT). (2) Non-invasive diagnostic tests encompassed 13/14 C-Urea Breath Test (UBT), SAT/serological antibody testing. Most studies used 13/14 C-UBT to assess the successful eradication of *H. pylori* infection at 4–12 weeks after the completion of therapy. (I) Intervention: VPZ-based treatment regimen, comprising various treatment durations (7 days, 10 days, or 14 days) and different drug dosages; (C) Comparator: control group receiving alternative therapies, including PPI triple 7-day therapy, PPI triple 14-day therapy, and PPI quadruple 14-day therapy; (O) Outcomes: primary outcome measure: *H. pylori* eradication rate based on Intention-to-treat (ITT) and Per-protocol (PP) analyses; secondary outcome measure: incidence of adverse events; (S) Study type: randomized controlled trials (RCTs). The detailed search strategy is outlined in Table 1 (PubMed is provided as an example).

Inclusion criteria

All papers underwent assessment by two independent researchers using pre-established criteria. The inclusion criteria were as follows: (1) Experimental group receiving various VPZ-based treatment regimens for *H. pylori* eradication; (2) Control group undergoing traditional PPI-based treatment protocols; (3) Clinical randomized controlled trials; (4) Outcome measures comprising eradication rates analyzed through Intention-to-treat analysis (ITT) or Per-protocol analysis (PP), alongside reports of adverse events. Two researchers independently assessed each paper and reconciled any disparities identified during the evaluation process through discussion.

Table 1 Search strategy on PubMed

#1	" H.pylori[MeSH Terms] "
#2	(((((H.pylori[Title/Abstract]) OR (Helicobacter nemestrinae[Title/Abstract])) OR (Campylobacter pylori[Title/Abstract])) OR (Campylobacter pylori subsp. pylori[Title/Abstract])) OR (Campylobacter pyloridis[Title/Abstract])
#3	(#1) OR (#2)
#4	" Vonoprazan"
#5	((((Vonoprazan[Title/Abstract]) OR (TAK 438[Title/Abstract])) OR (TAK-438[Title/Abstract])) OR (Takecab[Title/Abstract])) OR (potassium-competitive acid blocker[Title/Abstract])
#6	(#4) OR (#5)
#7	(#3) AND (#6)

Exclusion criteria

Studies with incomplete or unreported data were excluded. Similarly, studies from non-randomized controlled trials (including quasi-randomized controlled trials, protocols, conference abstracts, case reports, reviews, meta-analyses, animal studies, or correspondence) were also excluded. Additionally, studies that did not involve the intervention measures and results included in this review were excluded. Pilot studies were excluded as well.

Study selection

The literature was screened and excluded using the literature management software EndNote. Two researchers initially screened the literature titles, excluding duplicate publications and literature not pertinent to the research topic, such as non-randomized controlled trial studies, review papers, conference papers, protocols, and correspondence. Subsequently, the abstracts of the literature were reviewed by two researchers to identify relevant literature for inclusion and to exclude irrelevant literature. Finally, the remaining literature was read in full by both researchers, who further identified literature for inclusion. Throughout this process, both researchers independently screened the literature and subsequently compared the remaining literature; papers showing consistency were included in the final study, while any inconsistencies were discussed and resolved by a third researcher.

Data extraction

Two researchers independently performed data extraction, followed by content comparison. Data extraction was carried out using a standardized seven-item preselected form to record the following information for inclusion in the study: (1) First author, (2) Year of publication, (3) Country, (4) Study period, (5) Sample size, (6) Mean age, and (7) Detailed information on drug intervention measures, including drug type, dosage, frequency, and duration of administration.

Risk of bias of individual studies

In this study, all the literature included consisted of publicly published randomized controlled trials. We conducted a comprehensive risk of bias (ROB) assessment using the assessment tool outlined in the Cochrane Handbook 5.1.0 for randomized controlled trials (RCTs). Two researchers independently evaluated each piece of literature based on seven aspects: (1) Random sequence generation (selection bias), (2) Allocation concealment (selection bias), (3) Blinding of participants and personnel (performance bias), (4) Blinding of outcome assessment (detection bias), (5) Incomplete outcome data (attrition bias), (6) Selective reporting (reporting bias), and (7) Other bias. Based on the above seven aspects, the experiments are categorized into three levels of ROB: high (five or more aspects may have ROB), unclear (three or four aspects may have ROB), and low (two or less aspects may have ROB) (Fig. 1) [26].

Data analysis

The analysis of continuous variables holds paramount importance in drug intervention research. These variables are typically represented by standard deviation (SD) [27]. There are many treatment options for VPZ, and the aim of this study was to use NMA to make a direct and indirect comparison of different VPZ-based clinical randomised controlled trials to derive quantitative results and to rank the multiple treatment options, and thus to give recommendations for the best interventions. In our study, all variables are considered continuous and will be reported using multiple approaches. First, we will use Mean Difference (MD) to compare the absolute differences between the two groups. In addition, a 95% confidence interval (CI)

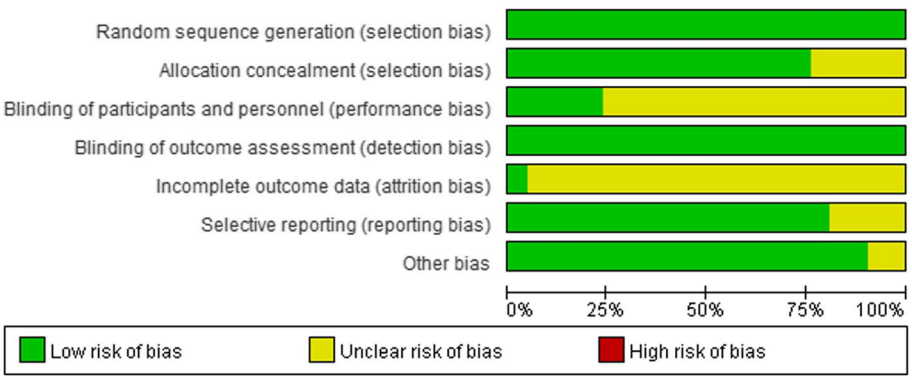

Fig. 1 Scheme of ROB assessment

will be provided to ascertain the accuracy and reliability of parameter estimation. Considering the potential differences between various studies, we opted for a random effects model for analysis rather than a fixed effects model [28].

We utilized Stata software (version 17.0) as the primary statistical analysis tool. The guiding principles of PRISMA NMA were adopted to apply a Bayesian-based framework for the aggregation and analysis process of NMA. The Bayesian approach is a statistical inference method that centers on the idea of describing uncertainty as a probability distribution and using Bayesian theory to update the probability distribution. Bayesian framework allows us to combine a priori information and observational data to more accurately estimate the effects and comparisons between different treatment options. The Markov Chain Monte Carlo Simulation Chain (MCMC) method was employed for parameter estimation [29, 30]. To quantify and demonstrate the consistency between indirect and direct comparisons, we employed the node method. Consistency and inconsistency tests were performed on all P-values for both indirect and direct comparisons among all studies regarding the eradication rate based on ITT and PP analyses. If the P-value is greater than 0.05, the consistency test will be considered passed, indicating that the results between direct and indirect comparisons are consistent [31].

In the generated network diagram, each node represents different treatment interventions, while the lines connecting the nodes represent direct head-to-head comparisons between interventions. The size of each node and the width of the connecting lines are directly proportional to the number of studies involved, aiding in observing the level of research support for different interventions [32].

When summarizing the intervention levels, they are reported as P-scores. The P-score resembles the surface under the cumulative ranking curve (SUCRA) value, which is used to assess the superiority of one treatment over others. SUCRA values across all competing treatments, ranging from 0 to 1. A score of 1 indicates the best treatment with no uncertainty, while a score of 0 indicates the worst treatment with no uncertainty. While SUCRA can indicate the need for re-evaluating intervention effectiveness or acceptability, caution is required when interpreting these scores, particularly if the actual clinical significance differences between interventions are insignificant [33]. To assess potential bias in small-scale studies that could contribute to publication bias in NMA, a network funnel plot was generated, and the shaping criteria were visually examined. This process entails assessing the symmetry of research results to identify potential unpublished studies or selective reporting [34].

Results

Study and identification and selection

A total of 1298 articles were retrieved from the electronic database, and an additional fourteen documents were manually searched by SCI-Hub, Google scholar, and Science direct, covering a total of 5481 samples (Supplementary Data). Subsequently, during the first round of screening of literature titles, 530 articles were excluded, leaving 293 articles retained. Following that, a second round of screening was performed based on the abstract content, resulting in the exclusion of 136 articles and retention of 157 articles. Lastly, a third round of screening was conducted by thoroughly reviewing the entire text. A total of 136 articles were excluded, with reasons including non-randomized controlled trials, incomplete data, meeting minutes, and failure to meet the required intervention measures for this review. In the end, 21 articles were identified as inclusion objects for the study (Fig. 2).

Quality assessment of the included studies

Among the studies we evaluated, 17 studies were categorized as low-risk, meaning they performed relatively well in terms of ROB in RCTs (Fig. 3). Additionally, 4 studies were classified as having unclear ROB, indicating a degree of uncertainty about their ROB. Encouragingly, none of the studies assessed were categorized as high ROB in our evaluation, suggesting overall high quality and reliability of the included studies.

However, despite the majority of studies being assessed as low-risk, only 5 studies achieved simultaneous blinding of participants and personnel. In other studies, achieving synchronous blinding of participants and personnel has become more challenging due to the use of oral medication as an intervention and the requirement for confirmation testing of *H. pylori* before treatment. This is because patients and their families must sign an informed consent form before the experiment begins, potentially revealing their understanding of the intervention measures and consequently impacting the implementation of blinding. One study employed a single-blind design, yet due to the aforementioned reasons, fully guaranteeing the blinding of the measurer is not feasible.

Characteristics of the included studies

A total of 21 RCTs were included, encompassing 5481 patients diagnosed with *H. pylori* positivity and investigating 12 eradication treatment options for *H. pylori*. The

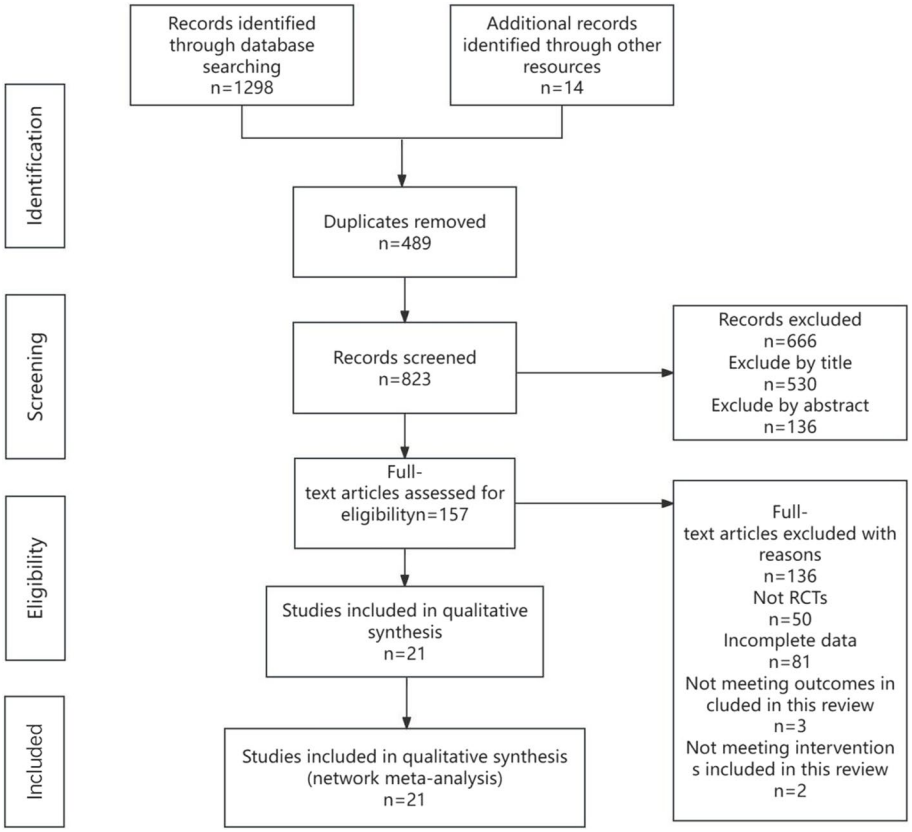

Fig. 2 Flow diagram of literature selection

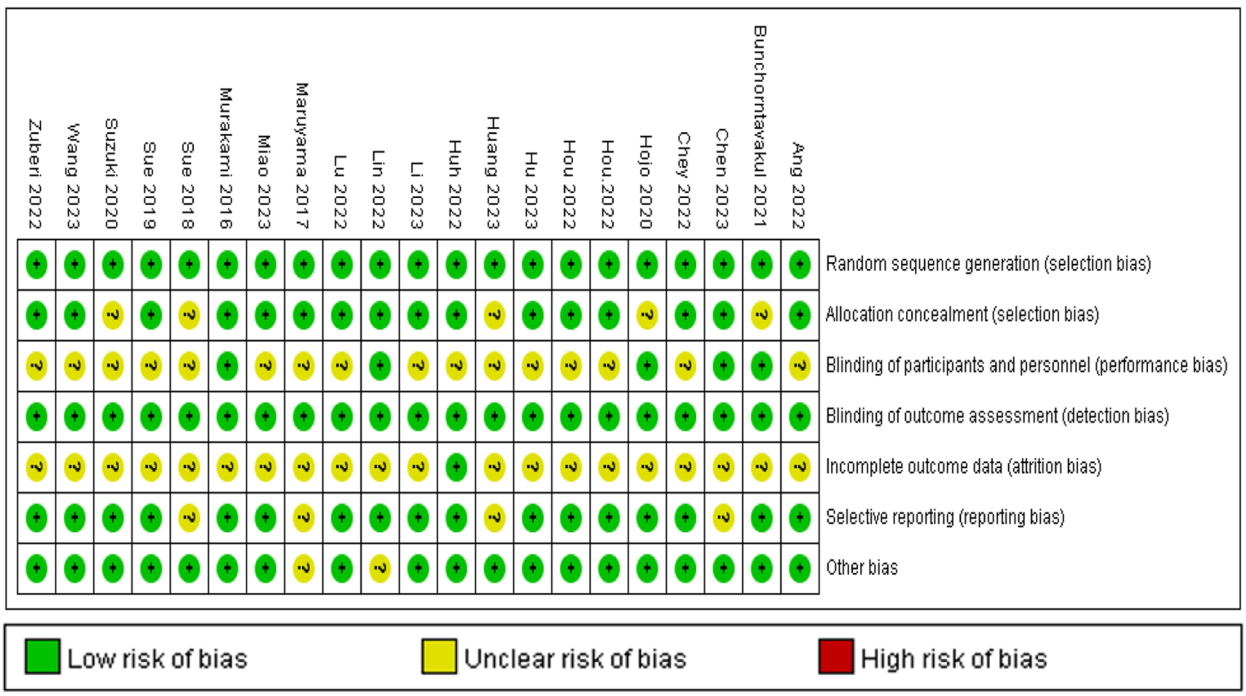

Fig. 3 Results of ROB assessment for 21 studies based on Cochrane risk assessment tool

interventions comprised low-dose VPZ dual 7-day therapy (L-VPZ-D7, 1 study) [35], VPZ dual 14-day therapy (VPZ-D14, 3 studies) [36–38], high-dose VPZ dual 14-day therapy (H-VPZ-D14, 3 studies) [21, 37, 39], VPZ triple 7-day therapy (VPZ-T7, 9 studies) [35, 40–47], VPZ triple 14-day therapy (VPZ-T14, 4 studies) [21, 38, 48, 49], VPZ quadruple 14-day therapy (VPZ-Q14, 7 studies) [48–54], high-dose VPZ dual 7-day therapy (H-VPZ-D7, 1 study) [47], VPZ dual 7-day therapy (VPZ-D7, 1 study) [47], VPZ quadruple 10-day therapy (VPZ-Q10, 1 study) [53]. ITT analysis was reported as the outcome measure in 21 studies, while PP analysis was reported in 15 studies. The included studies comprised 17 from East Asia (Japan, China, Korea), 1 from the United States (USA), 2 from Southeast Asia (Singapore, Thailand), and 1 from South Asia (Pakistan). The characteristics of the included studies are shown in Table 2.

Network meta-analysis

The complete NMA figures are presented in Fig. 4a and b, which indicates that the most common treatment plans for eradicating *H. pylori* infection include the bismuth-based PPI quadruple 14-day (PPI-Q14) treatment plan, VPZ-Q14 treatment plan, VPZ-T7 plan, and VPZ-T14 plan. These treatment plans have undergone extensive study and demonstrate dense connectivity within the network. Particularly, there are direct head-to-head comparisons between VPZ-Q14 and PPI-Q14, as well as between VPZ-T7 and PPI triple 7-day (PPI-T7). Moreover, a substantial number of studies support these comparisons, offering ample data for further analysis.

Eradication rate in ITT analysis

As displayed in Tables 3 and 4, VPZ-Q14 therapy showed the most significant advantage according to ITT analysis, indicating a notably higher efficacy in eradicating *H. pylori* compared to PPI-based therapies. Additionally, other VPZ treatment regimens, including VPZ-Q10, VPZ-T14, VPZ-D14, H-VPZ-D14, and H-VPZ-D7, exhibited substantial eradication effects. In contrast, the efficacy of PPI-T7 in eradicating *H. pylori* was comparatively lower.

As illustrated in Fig. 5; Table 5, the probability ranking of the effectiveness in ITT of different treatment interventions indicates that VPZ-Q14 therapy ranks first in SUCRA (0.874). The SUCRA rankings of other therapies are as follows: VPZ-Q10 > VPZ-T14 > VPZ-D14 = H-VPZ-D14 > H-VPZ-D7 > PPI-Q14 > VPZ-T7 > VPZ-D7 > PPI-T14 > L-VPZ-D7 > > PPI-T7. The SUCRA of VPZ-Q14 (0.874) was higher than that of VPZ-Q10 (0.818), indicating the more significant beneficial effect of VPZ-Q14 on patients with *H. pylori* infection. Whereas, the MD of VPZ-Q14 (6.48) was lower than that of VPZ-Q10 (7.57), suggesting the more concentrated data and the less variation in VPZ-Q14 treated group.

Eradication rate in PP analysis

According to PP analysis (Tables 6 and 7), the results revealed significant advantages of VPZ-Q10 over PPI-based therapy in eradicating *H. pylori* infection, with an average difference of MD = 7.03, 95% CI = (0.63, 78.79). Moreover, VPZ-Q14 exhibited an average difference compared to VPZ-T14 and PPI-based therapies, demonstrating significant positive effects. Additionally, VPZ-D7, VPZ-T7, and H-VPZ-D7 showed good efficacy, PPI-T14 and PPI-T7 showed certain advantages. Conversely, PPI-Q14, L-VPZ-D7, and VPZ-D14 exhibited slightly inferior effects, albeit with a certain degree of improvement.

The probability ranking of effectiveness in PP analysis of various treatment interventions reveals that VPZ-Q10 ranks first in SUCRA (0.849, as depicted in Fig. 6). Following closely are VPZ-Q14, VPZ-T14, and VPZ-D7, with SUCRA scores of 0.759, 0.599, and 0.587, respectively. This indicates the favorable performance of these treatment plans in terms of effectiveness. Overall, the VPZ treatment regimen demonstrated superior ranking and probability in PP analysis, further affirming its potential as a preferred treatment option.

Safety evaluation

The study primarily documented mild drug-related adverse effects, encompassing gastrointestinal symptoms like diarrhea, abdominal pain, bloating, constipation, nausea and vomiting, belching, and taste abnormalities (bitterness), alongside occasional discomforts such as fever and rash. Notably, the top five regimens in this study based on SUCRA values were all regimens with a treatment duration of 10 or 14 days. Therefore, we will focus on evaluating the overall incidence of adverse effects of H-VPZ-D14, VPZ-Q14, VPZ-Q10, VPZ-T14, VPZ-D14, and PPI-Q14 for safety.

As shown in Fig. 7; Table 8, VPZ-based therapies showed a significant advantage over PPI-Q14 therapy in the incidence of adverse effects, especially H-VPZ-D14, with an average difference of MD = 0.02, 95% CI = (0.00, 0.63). According to the probability ranking of safety, H-VPZ-D14 therapy ranked first in SUCRA, reaching 0.952 (Fig. 8), indicating that it is a safer option with a relatively low incidence of adverse effect. The SUCRA rankings of other therapies are as follows: VPZ-T14 (0.664) > VPZ-D14 (0.655) > VPZ-Q14

Table 2 Characteristics of the studies included in the meta-analysis

Author	Country	Year	Population	Age (mean + SD)	Total/male/female	Intervention	Control	Outcome (ITT)
Murakami [40]	Japan	2016	Patients with HP+	T: 55.2(12.3) C:53.9(12.9)	T: 329/196/133 C:321/194/127	VPZ triple therapy (VPZ, AMO, CLR) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg, CLR 200 mg/400 mg Freq: 2 times a day	PPI triple therapy (LPZ, AMO, CLR) Length of Intervention: 7 days Dose: LPZ 30 mg, AMO 750 mg, CLR 200 mg/400 mg Freq: 2 times a day	T: 92.6% C: 75.9%
Maruyama [41]	Japan	2017	Patients with HP+	T:58 (32–80) C: 60 (36–77)	T: 72/41/31 C: 69/40/29	VPZ triple therapy (VPZ, AMO, CLR) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg, CLR 200/400 mg Freq: 2 times a day	PPI triple therapy (RPZ/LPZ, AMO, CLR) Length of Intervention: 7 days Dose: RPZ 20 mg/LPZ 30 mg, AMO 750 mg, CLR 200/400 mg Freq: 2 times a day	T: 95.8% C: 69.6%
Sue [42]	Japan	2018	Patients with HP+	T: 64.3(12.3) C: 61.9(13.3)	T: 55/37/18 C:51/35/16	VPZ triple therapy (VPZ, AMO, CLR) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg, CLR 200/400 mg Freq: 2 times a day	PPI triple therapy (LPZ/RPZ/EPZ, AMO, CLR) Length of Intervention: 7 days Dose: LPZ 30 mg /RPZ 10 mg/EPZ 20 mg, AMO 750 mg, CLR 200/400 mg Freq: 2 times a day	T: 87.3% C: 76.5%
Sue [43]	Japan	2019	Patients with HP+	T: 62.4(14.1) C: 64.0(12.3)	T: 33/18/15 C: 30/15/15	VPZ triple therapy (VPZ, AMO, STFX) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg, STFX 100 mg Freq: 2 times a day	PPI triple therapy (EPZ/RPZ/LPZ, AMO, STFX) Length of Intervention: 7 days Dose: EPZ 20 mg/RPZ 10 mg/LPZ 30 mg, AMO 750 mg, STFX 100 mg Freq: 2 times a day	T: 75.8% C: 53.3%
Suzuki [35]	Japan	2020	Patients with HP+	T: 61.2(11.5) C: 61.3(10.4)	T: 168/106/62 C: 167/103/64	VPZ dual low dose Therapy (VPZ, AMO) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg Freq: 2 times a day	VPZ triple therapy (VPZ, AMO, CLR) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg, CLR 200 mg Freq: 2 times a day	T: 84.5% C: 89.2%

Table 2 (continued)

Author	Country	Year	Population	Age (mean + SD)	Total/male/female	Intervention	Control	Outcome (ITT)
Hojo [44]	Japan	2020	Patients with HP+	T: 56.0(10.9) C: 57.2(14.4)	T: 23/12/11 C: 23/14/9	VPZ triple therapy (VPZ, AMO, MNZ) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg, MNZ 250 mg Freq: 2 times a day	PPI triple therapy (RPZ, AMO, MNZ) Length of Intervention: 7 days Dose: RPZ 10 mg, AMO 750 mg, MNZ 250 mg Freq: 2 times a day	T: 73.9% C: 82.6%
Bunchorntavakul [45]	Thailand	2021	Patients with HP+	T: 54.21(12.3) C: 56.79(13.25)	T: 61/26/35 C: 61/31/30	VPZ triple therapy (VPZ, AMO, CLR) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 1000 mg, CLR 500 mg Freq: 2 times a day	PPI triple therapy (OPZ, AMO, CLR) Length of Intervention: 14 days Dose: OPZ 20 mg, AMO 1000 mg, CLR 500 mg Freq: 2 times a day	T: 96.7% C: 88.5%
Hou [51]	China	2022	Patients with HP+	T: 44.9(13.3) C: 44.6(14.1)	T: 311/209/102 C: 318/220/98	VPZ quadruple therapy (VPZ, AMO, CLR, BPC/BTD) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg, CLR 500 mg, BPC/BTD 600 mg Freq: 2 times a day	PPI quadruple therapy (LPZ, AMO, CLR, BPC/BTD) Length of Intervention: 14 days Dose: LPZ 30 mg, AMO 1000 mg, CLR 500 mg, BPC/BTD 600 mg Freq: 2 times a day	T: 90.6% C: 85.2%
Ang [46]	Singapore	2022	Patients with HP+	T: 51.5 (14.7) C: 52.0 (14.6)	T: 119/68/51 C: 125/82/43	VPZ triple therapy (VPZ, AMO, CLR) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 1000 mg, CLR 500 mg Freq: 2 times a day	PPI triple therapy (OPZ/EPZ/RPZ, AMO, CLR) Length of Intervention: 14 days Dose: OPZ/EPZ/RPZ 20 mg, AMO 1000 mg, CLR 500 mg Freq: 2 times a day	T: 87.4% C: 88.0%
Chey [21]	USA	2022	Patients with HP+	T: 51.8 (13.6) C: 50.6(13.9)	T: 324/128/196 C: 338/118/220	VPZ dual high-dose therapy (VPZ, AMO) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg Freq: VPZ 2 times a day, AMO 3 times a day	VPZ/PPI triple therapy (VPZ/LPZ, AMO, CLR) Length of Intervention: 14 days Dose: VPZ 20 mg/LPZ 30 mg, AMO 1000 mg, CLR 500 mg Freq: 2 times a day	T: 77.2% C: 80.8%

Table 2 (continued)

Author	Country	Year	Population	Age (mean + SD)	Total/male/female	Intervention	Control	Outcome (ITT)
Hou [52]	China	2022	Patients with HP+	T: 42.0 (12.18) C: 41.4 (12.89)	T: 265/166/99 C: 268/176/92	VPZ quadruple therapy (VPZ, AMO, CLR, BPC/BTD) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg, CLR 500 mg, BPC/BTD 600 mg Freq: 2 times a day	PPI quadruple therapy (LPZ, AMO, CLR, BPC/BTD) Length of Intervention: 14 days Dose: LPZ 30 mg, AMO 1000 mg, CLR 500 mg, BPC/BTD 600 mg Freq: 2 times a day	T: 91.5% C: 86.8%
Huh [50]	Korea	2022	Patients with HP+	T: 32.8(6.9) C: 33.3(8.6)	T: 15/14/1 C: 15/14/1	VPZ quadruple therapy VPZ, AMO, CLR, Bismuth) Length of Intervention: 14 days Dose: VPZ 20 mg, Bismuth 220 mg, CLR 500 mg, AMO 1000 mg Freq: 2 times a day	PPI quadruple therapy (LPZ, AMO, CLR, Bismuth) Length of Intervention: 14 days Dose: LPZ 30 mg, Bismuth 220 mg, CLR 500 mg, AMO 1000 mg Freq: 2 times a day	T: 80% C: 93.3%
Lin [47]	China	2022	Patients with HP+	T: 43(31, 52)/ 40 (32, 50) C: 39 (30, 50)	T: 85/38/47 84/31/53 C: 61/28/33	VPZ dual high-dose therapy (VPZ, AMO) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg VPZ dual therapy (VPZ, AMO) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 500 mg Freq: VPZ 2 times a day, AMO 3 times a day	VPZ triple therapy (VPZ, AMO, CLR) Length of Intervention: 7 days Dose: VPZ 20 mg, AMO 750 mg, CLR 500 mg Freq: 2 times a day	T: 63.5%/58.3% C: 60.7%

Table 2 (continued)

Author	Country	Year	Population	Age (mean + SD)	Total/male/female	Intervention	Control	Outcome (ITT)
Lu [53]	China	2023	Patients with HP+	T: 37.14(19.65)/35.88 (11.51) C: 36.54 (10.96)	T: 78/32/46 78/37/41 C: 78/34/44	VPZ quadruple therapy (VPZ, AMO, FZD, Colloidal bismuth) Length of Intervention: 10/14 days Dose: VPZ 20 mg, AMO 1000 mg, FZD 100 mg, colloidal bismuth 200 mg Freq: 2 times a day	PPI quadruple therapy (EPZ, AMO, FZD, CBT) Length of Intervention: 14 days Dose: EPZ 20 mg, AMO 1000 mg, FZD 100 mg, CBT 200 mg Freq: 2 times a day	T: 96.2%/94.9% C: 93.6%
Zuberi [36]	Pakistan	2022	Patients with HP+	T: 41.4(10.6) C: 40.2(9.8)	T: 92/55/37 C: 87/54/33	VPZ dual therapy (VPZ, AMO) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg Freq: 2 times a day	PPI triple therapy (OPZ, AMO, CLR) Length of Intervention: 14 days Dose: AMO 1000 mg, CLR 500 mg, OPZ 20 mg Freq: 2 times a day	T: 93.5% C: 83.9%
Chen [49]	China	2023	Patients with HP+	T: 44.36(12.40) 46.49(11.60) C: 44.29(12.10)	T: 100/42/58 100/41/59 C: 100/47/53	VPZ berberine triple therapy (VPZ, Berberine, AMO) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg, Berberine 500 mg VPZ quadruple therapy (VPZ, AMO, CLR, CBT) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg, CLR 500 mg, CBT 220 mg Freq: 2 times a day	PPI quadruple therapy (RPZ, AMO, CLR, CBT) Length of Intervention: 14 days Dose: RPZ 10 mg, AMO 1000 mg, CLR 500 mg, CBT 220 mg Freq: 2 times a day	T: 70.0%/77.0% C: 69.0%
Hu [37]	China	2023	Patients with HP+	T: 41.1(12.1) C:40.1(13.1)	T: 55/22/33 C: 55/27/28	VPZ dual therapy (VPZ, AMO) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg Freq: 2 times a day	VPZ dual high-dose therapy (VPZ, AMO) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg Freq: VPZ 2 times a day, AMO 3 times a day	T: 89.1% C: 87.3

Table 2 (continued)

Author	Country	Year	Population	Age (mean + SD)	Total/male/female	Intervention	Control	Outcome (ITT)
Huang [48]	China	2023	Patients with HP+	T: 52.14(5.37)/ 51.36(3.94) C: 50.82(4.83)	T: 40/23/17 40/22/18 C: 40/25/15	VPZ triple therapy (VPZ, AMO, BPC) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg, BPC 600 mg VPZ quadruple therapy (VPZ, AMO, FZD, BPC) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg, FZD 100 mg, BPC 600 mg Freq: 2 times a day	PPI quadruple therapy (EPZ, AMO, FZD, BPC) Length of Intervention: 14 days Dose: EPZ 20 mg, AMO 1000 mg, FZD 100 mg, BPC 600 mg Freq: 2 times a day	T: 95%/97.5% C: 80%
Li [38]	China	2023	Patients with HP+	T: 45.85(13.97)/ 43.85(15.47) C: 42.67(12.61)	T: 75/26/49 74/31/43 C: 75/34/41	VPZ dual therapy (VPZ, AMO) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 750 mg VPZ Jing hua Wei kang triple therapy (VPZ, AMO, Jing hua Wei kang Capsule) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 750 mg, Jing hua Wei kang Capsule 160 mg Freq: VPZ 2 times a day, AMO three times a day, Jing hua Wei kang Capsule 3 times a day	PPI quadruple therapy (EPZ, AMO, FZD, BPC) Length of Intervention: 14 days Dose: EPZ 20 mg, AMO 1000 mg, FZD 100 mg, BPC 600 mg Freq: 2 times a day	T: 77.33%/86.49% C: 78.67%
Miao [54]	China	2023	Patients with HP+	T: 34.5(9.6) C: 31.6(9.6)	T: 22/14/8 C: 22/13/9	VPZ quadruple therapy (VPZ, AMO, CLR, BPC) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 1000 mg, CLR 500 mg, BPC 600 mg Freq: 2 times a day	PPI quadruple therapy (EPZ, AMO, CLR, BPC) Length of Intervention: 14 days Dose: EPZ 20 mg, AMO 1000 mg, CLR 500 mg, BPC 600 mg Freq: 2 times a day	T: 100% C: 94.4%

Table 2 (continued)

Author	Country	Year	Population	Age (mean + SD)	Total/male/female	Intervention	Control	Outcome (ITT)
Wang [39]	China	2023	Patients with HP+	T: 44.2 ± 10.8 C: 44.5 ± 8.8	T: 74/36/38 C: 77/34/43	VPZ dual high-dose therapy (VPZ, AMO) Length of Intervention: 14 days Dose: VPZ 20 mg, AMO 750 mg Freq: VPZ 2 times a day, AMO 4 times a day	PPI quadruple therapy (RPZ, AMO, CLR, BPC) Length of Intervention: 14 days Dose: RPZ 10 mg, AMO 1000 mg, CLR 500 mg, BPC 220 mg Freq: 2 times a day	T: 94.6% C: 87.0%

Dual therapy: 2000–2250 mg per day, Dual high-dose therapy: 3000 mg per day. Dual low-dose therapy: 1500 mg per day

T Experimental group, *C* Control group, *VPZ* Vonoprazan, *AMO* Amoxicillin, *CLR* Clarithromycin, *RPZ* Rabeprazole, *LPZ* Lansoprazole, *EPZ* Esomeprazole, *STFX* Sitafloxacin, *MNZ* Metronidazole, *OPZ* Omeprazole, *BPC* Bismuth potassium citrate, *BTD* Bismuth tripotassium dicitrate, *FZD* Furazolidone, *CBT* Colloidal bismuth tartrate

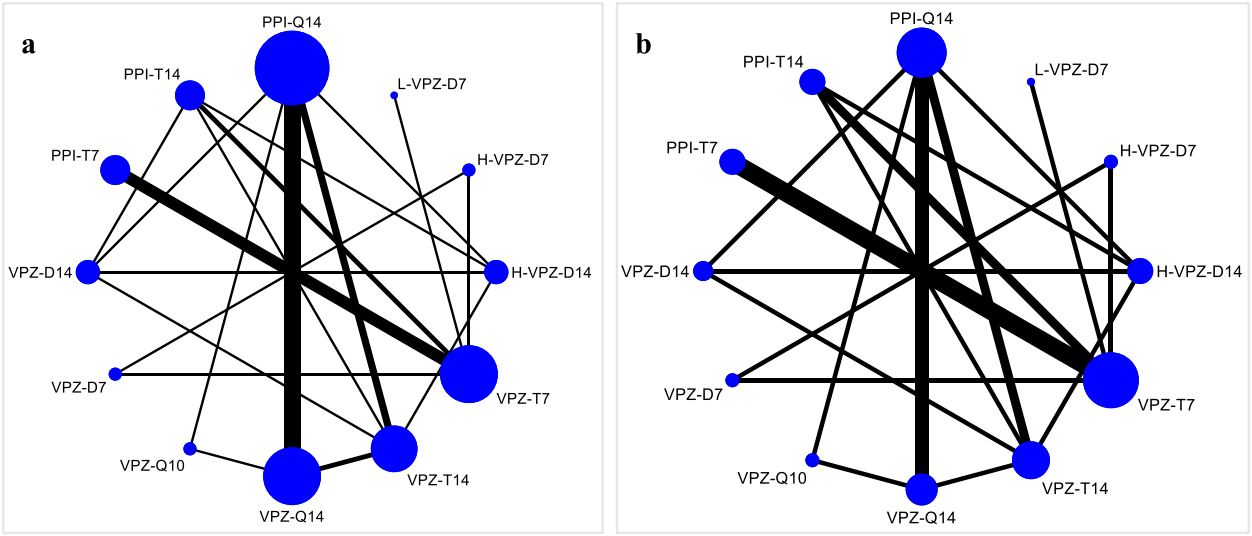

Fig. 4 *H. pylori* eradication rate of VPZ- and PPI-based treatments in (**a**) ITT and (**b**) PP analyses (L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days)

(0.398) > PPI-Q14 (0.228) > VPZ-Q10 (0.103). Despite the ranking, VPZ-T14 and VPZ-D14 still demonstrate the acceptable level of security. In contrast, PPI-Q14 and VPZ-Q10 showed relatively high adverse effects.

Publication bias test

We meticulously developed individual funnel plots for each outcome measure. Upon visual examination of these plots, no significant publication bias was observed, suggesting a certain level of credibility and rigor in the selected research data. Further details are depicted in Fig. 9.

Discussion

This study aimed to assess the efficacy of various VPZ-based therapies compared to traditional PPI-based therapies in eradicating *H. pylori* infection. A total of 21 studies, encompassing 12 distinct treatment options, were included, involving 5481 patients diagnosed with *H. pylori* infection, indicating a substantial sample size. Our findings indicate that VPZ-Q14 and VPZ-Q10 demonstrate a statistically significant beneficial effect on patients with *H. pylori* infection compared to other treatment options and the control group. First, overall, the VPZ-based treatment regimen exhibits significantly higher efficacy in *H. pylori* eradication compared to the PPI-based regimen. Second, based on ITT analysis, VPZ-Q14 emerges as the optimal intervention. Conversely, according to PP analysis, VPZ-Q10 proves to be the most effective intervention. Regarding safety, no experiments reported significant adverse effects related to the drug. In comparison with PPI-based treatment regimens, VPZ-based regimens demonstrate a lower overall incidence of adverse reactions. The occurrence of adverse reactions in both the VPZ-Q14 and VPZ-Q10 regimens is deemed acceptable. Overall, we suggest that a 14-day or 10-day eradication plan based on VPZ may represent the most suitable intervention for managing *H. pylori* infection.

In clinical epidemiology, experimental studies typically adopt the form of RCTs. Data analysis of RCTs can be performed using two complementary strategies: ITT analysis and PP analysis. In fact, according to the CPMP guidelines [55], "in non-inferiority trials, ITT and PP analysis hold equal significance, and their results should yield analogous conclusions to furnish a compelling interpretation". In this scenario, ITT analysis should remain the primary analysis as it preserves the advantage of randomization, while PP analysis can serve as a supportive sensitivity analysis for non-inferiority and equivalence studies [56]. Overall, both ITT and PP analyses are efficacious, however, their scope and interpretation vary.

Our research concludes that a 14-day or 10-day therapy based on VPZ may represent the most suitable intervention for improving *H. pylori* infection, which is similar to the conclusion of the reported work [57, 58]. Therefore, our researchers sought to investigate the potential impact of enhancing subjects' compliance

Table 3 VPZ- and PPI-based treatments for *H. Pylori* eradication rate in ITT analysis with mean difference (MD) and 95% confidence interval (CI) values[a].

VPZ-Q14	VPZ-Q10	VPZ-T14	VPZ-D14	H-VPZ-D14	H-VPZ-D7	PPI-Q14	VPZ-T7	VPZ-D7	PPI-T14	L-VPZ-D7	PPI-T7
VPZ-Q14	1.17 (0.30,4.52)	0.84 (0.53,1.33)	0.69 (0.37,1.31)	0.69 (0.40,1.19)	0.58 (0.19,1.75)	0.60 (0.44,0.81)	0.51 (0.21,1.23)	0.46 (0.15,1.40)	0.42 (0.24,0.72)	0.34 (0.11,1.01)	0.15 (0.06,0.40)
0.86 (0.22,3.31)	VPZ-Q10	0.72 (0.18,2.92)	0.59 (0.14,2.57)	0.59 (0.14,2.47)	0.49 (0.09,2.78)	0.51 (0.13,1.97)	0.44 (0.09,2.15)	0.40 (0.07,2.23)	0.36 (0.09,1.50)	0.29 (0.05,1.61)	0.13 (0.03,0.68)
1.19 (0.75,1.89)	1.39 (0.34,5.66)	VPZ-T14	0.83 (0.48,1.43)	0.82 (0.59,1.16)	0.69 (0.25,1.92)	0.71 (0.47,1.07)	0.61 (0.28,1.32)	0.55 (0.20,1.53)	0.50 (0.36,0.70)	0.40 (0.15,1.10)	0.18 (0.08,0.43)
1.44 (0.76,2.72)	1.68 (0.39,7.29)	1.21 (0.70,2.09)	VPZ-D14	1.00 (0.57,1.76)	0.83 (0.27,2.55)	0.86 (0.48,1.54)	0.74 (0.30,1.80)	0.67 (0.22,2.04)	0.61 (0.35,1.06)	0.49 (0.16,1.46)	0.22 (0.08,0.58)
1.45 (0.84,2.48)	1.69 (0.40,7.05)	1.21 (0.86,1.71)	1.00 (0.57,1.77)	H-VPZ-D14	0.84 (0.30,2.32)	0.86 (0.53,1.41)	0.74 (0.35,1.59)	0.67 (0.24,1.86)	0.61 (0.44,0.84)	0.49 (0.18,1.33)	0.22 (0.10,0.52)
1.73 (0.57,5.25)	2.02 (0.36,11.37)	1.45 (0.52,4.04)	1.20 (0.39,3.67)	1.20 (0.43,3.32)	H-VPZ-D7	1.03 (0.35,3.06)	0.89 (0.45,1.75)	0.80 (0.43,1.49)	0.73 (0.28,1.91)	0.59 (0.23,1.49)	0.27 (0.12,0.58)
1.68 (1.24,2.28)	1.96 (0.51,7.55)	1.41 (0.93,2.12)	1.16 (0.65,2.08)	1.16 (0.71,1.89)	0.97 (0.33,2.87)	PPI-Q14	0.86 (0.37,2.01)	0.78 (0.26,2.30)	0.70 (0.43,1.16)	0.57 (0.20,1.65)	0.26 (0.10,0.66)
1.95 (0.81,4.69)	2.28 (0.46,11.15)	1.64 (0.76,3.52)	1.35 (0.56,3.29)	1.35 (0.63,2.89)	1.13 (0.57,2.22)	1.16 (0.50,2.72)	VPZ-T7	0.91 (0.46,1.77)	0.82 (0.41,1.63)	0.66 (0.35,1.26)	0.30 (0.21,0.44)
2.15 (0.71,6.51)	2.52 (0.45,14.12)	1.81 (0.65,5.01)	1.49 (0.49,4.56)	1.49 (0.54,4.12)	1.24 (0.67,2.31)	1.28 (0.43,3.80)	1.10 (0.56,2.16)	VPZ-D7	0.90 (0.34,2.37)	0.73 (0.29,1.85)	0.33 (0.15,0.72)
2.38 (1.38,4.10)	2.78 (0.67,11.64)	2.00 (1.43,2.79)	1.65 (0.94,2.90)	1.65 (1.19,2.28)	1.38 (0.52,3.62)	1.42 (0.86,2.34)	1.22 (0.61,2.44)	1.11 (0.42,2.90)	PPI-T14	0.81 (0.31,2.07)	0.37 (0.17,0.81)
2.95 (0.99,8.78)	3.45 (0.62,19.15)	2.48 (0.91,6.74)	2.05 (0.68,6.14)	2.04 (0.75,5.54)	1.71 (0.67,4.34)	1.76 (0.61,5.12)	1.52 (0.80,2.88)	1.37 (0.54,3.48)	1.24 (0.48,3.18)	L-VPZ-D7	0.46 (0.22,0.96)
6.48 (2.50,16.84)	7.57 (1.48,38.72)	5.44 (2.32,12.75)	4.49 (1.71,11.80)	4.48 (1.92,10.49)	3.74 (1.73,8.11)	3.87 (1.53,9.79)	3.32 (2.29,4.83)	3.01 (1.39,6.49)	2.72 (1.24,5.96)	2.19 (1.04,4.61)	PPI-T7

[a] L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days

Table 4 MD and 95% CI values of VPZ- and PPI-based treatments in ITT analysis[a].

Intervention	MD	95% CI
VPZ-Q14	6.48	(2.50, 16.84)
VPZ-Q10	7.57	(1.48, 38.72)
VPZ-T14	5.44	(2.32, 12.75)
VPZ-D14	4.49	(1.71, 11.80)
H-VPZ-D14	4.48	(1.92, 10.49)
H-VPZ-D7	3.74	(1.73, 8.11)
PPI-Q14	3.87	(1.53, 9.79)
VPZ-T7	3.32	(2.29, 4.83)
VPZ-D7	3.01	(1.39, 6.49)
PPI-T14	2.72	(1.24, 5.96)
L-VPZ-D7	2.19	(1.04, 4.61)
PPI-T7	0.46	(0.22, 0.96)

[a] L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days

with the research protocol on treatment efficacy. Through ITT analysis, the efficacy of VPZ therapy over 14 days was evident; however, in actuality, this treatment proved more efficacious for participants who fully adhered to the study protocol. Conversely, PP analysis indicated that therapy lasting 10 days yielded clearer effectiveness. These PP results hypothesize that improved adherence to the experimental drug may lead to more favorable clinical treatment outcomes. Thus, compliance emerges as a pivotal variable for the success of quadruple therapy. Enhanced compliance not only ensures a high eradication rate but also reduces medication cycles and costs. Studies indicate that treatment adherence below 80% has been associated with reduced treatment success rates [59]. Regarding the reasons for low compliance, multiple factor analysis revealed that the primary reason for patients not adhering to treatment is side effects. Antibiotic treatment in eradication regimens can readily induce a range of short-term side effects, including diarrhea, nausea, vomiting, bloating, or abdominal pain [60]. Therefore, optimizing eradication therapy

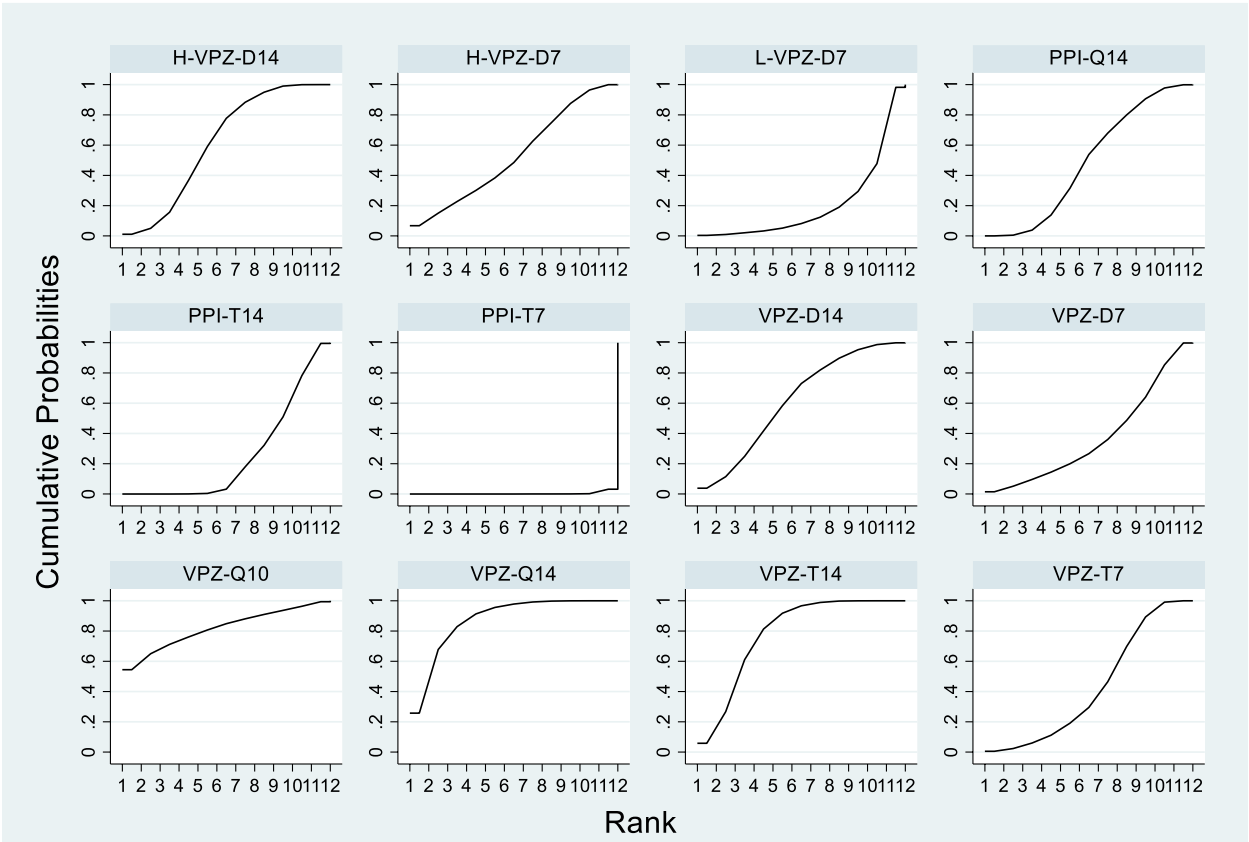

Fig. 5 SUCRA plots for eradication rate of VPZ- and PPI-based treatments in ITT analysis (L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days)

Table 5 SUCRA scores of VPZ- and PPI-based treatments in ITT analysis[a].

Intervention	SUCRA
VPZ-Q14	0.874
VPZ-Q10	0.818
VPZ-T14	0.782
VPZ-D14	0.617
H-VPZ-D14	0.617
H-VPZ-D7	0.531
PPI-Q14	0.493
VPZ-T7	0.432
VPZ-D7	0.372
PPI-T14	0.258
L-VPZ-D7	0.205
PPI-T7	0.004

[a] L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days

and reducing antibiotic misuse can, to some extent, mitigate adverse reactions, enhance patient compliance, decrease treatment duration and medication expenses, elevate eradication rates, and diminish recurrence. A study revealed that following a one-year follow-up of patients who successfully eradicated *H. pylori* infection, the one-year recurrence rate of *H. pylori* infection after eradication in the coastal provinces of southern China was 3.5%. Key independent factors influencing *H. pylori* recurrence encompass contact with infected individuals, unsatisfactory hygiene conditions in dining areas, consumption of contaminated water, frequent dining out, and irregular dietary patterns [61]. Therefore, successful eradication of *H. pylori* infection should also entail controlling and reducing the recurrence rate.

According to the results of the network meta-analysis, VPZ-T14 therapy emerged as one of the top three effective interventions based on both ITT and PP analyses. Among the therapies we incorporated, triple therapy consisted of a combination of VPZ-AMO-CLR and a combination of VPZ-AMO-traditional Chinese medicine preparations (berberine and Jinghua Weikang capsules). Notably, all therapies employed AMO. In theory, AMO represents an almost ideal antibacterial agent due to its bactericidal properties, with resistance occurrences being rare even in cases of treatment failure [62]. A meta-analysis on primary antibiotic resistance of *H. pylori* in the Asia Pacific region indicated very low resistance rates of *H. pylori* to AMO and tetracycline (TET). In China, the rates are 3.1% and 3.9%, respectively; in Japan, they are 3.0% and 2.0%, respectively; and in South Korea, they are 9.5% and 0%, respectively [63]. However, for CLR with a high resistance rate, research in Japan has shown that the benefits of adding CLR to VPZ-AMO combination are minimal. Therefore, the combination of antibiotic abuse and low cure rates suggests that VPZ-CLR triple therapy should not be used for *H. pylori* infection. Removing CLR, VPZ-AMO dual therapy has been proven effective in other places, and after optimization, it may ultimately prove useful in the United States/Europe [64]. Thus, the strategy of eliminating CLR and incorporating traditional Chinese medicine preparations into VPZ triple therapy appears to mitigate antibiotic abuse while enhancing the cure rate, offering comparable advantages to VPZ-AMO dual therapy. Nevertheless, additional research is warranted to ascertain whether it delivers superior antibacterial effects and safety profiles compared to dual therapy. Consequently, alongside the favored quadruple therapy, traditional Chinese medicine triple therapy emerges as a potential approach for *H. pylori* eradication, meriting further investigation.

In summary, our study holds clinical significance in several aspects. First, despite the satisfactory results of VPZ-based therapy in eradicating *H. pylori* infection, its approval for this purpose remains limited in most countries and regions. This study could serve as a guiding reference in these areas. Secondly, while research on eradicating *H. pylori* infection through VPZ is primarily concentrated in the United States and Asian countries like Japan, China, and South Korea. With the Asian continent's population alone exceeding 2 billion, presenting a considerable sample size, and the highly convincing conclusions drawn from RCTs, clinical practitioners can consider employing VPZ quadruple therapy for either 14 or 10 days in treating *H. pylori* infection patients with comparable drug resistance rates in the region. Alternatively, they may explore further optimization of VPZ-based therapy to enhance treatment outcomes.

Strengths and limitations

Firstly, our study encompassed 21 RCTs involving 5481 patients, thus offering more robust evidence-based recommendations.

Secondly, numerous studies on the eradication of *H. pylori* infection using VPZ have been reported. For example, the efficacy and safety of low- and high-dose amoxicillin in VPZ-amoxicillin dual therapy were evaluated [57]. It concluded that low-dose amoxicillin (VLA) therapy demonstrated comparable efficacy and safety to high-dose amoxicillin (VHA) therapy. Another work

Table 6 VPZ- and PPI-based treatments for *H. Pylori* eradication rate in PP analysis with mean difference (MD) and 95% confidence interval (CI) values[a]

VPZ-Q10	VPZ-Q14	VPZ-T14	VPZ-D7	VPZ-T7	H-VPZ-D7	H-VPZ-D14	PPI-Q14	L-VPZ-D7	VPZ-D14	PPI-T14	PPI-T7
VPZ-Q10	0.48 (0.05,4.49)	0.33 (0.03,3.20)	0.32 (0.02,5.90)	0.31 (0.02,4.63)	0.31 (0.02,5.61)	0.29 (0.03,3.25)	0.27 (0.03,2.42)	0.22 (0.01,4.07)	0.18 (0.02,2.12)	0.14 (0.01,1.59)	0.11 (0.01,1.76)
2.07 (0.22,19.20)	VPZ-Q14	0.67 (0.26,1.76)	0.67 (0.09,5.12)	0.63 (0.11,3.67)	0.64 (0.08,4.87)	0.60 (0.17,2.10)	0.57 (0.24,1.35)	0.47 (0.06,3.53)	0.37 (0.09,1.46)	0.29 (0.08,1.02)	0.22 (0.03,1.48)
3.07 (0.31,30.19)	1.48 (0.57,3.87)	VPZ-T14	1.00 (0.16,6.11)	0.94 (0.21,4.22)	0.95 (0.15,5.81)	0.89 (0.37,2.17)	0.84 (0.38,1.87)	0.69 (0.11,4.21)	0.55 (0.18,1.65)	0.44 (0.19,1.02)	0.32 (0.06,1.74)
3.08 (0.17,55.97)	1.49 (0.20,11.36)	1.00 (0.16,6.16)	VPZ-D7	0.94 (0.34,2.62)	0.95 (0.36,2.54)	0.90 (0.15,5.31)	0.84 (0.12,5.91)	0.69 (0.16,2.91)	0.55 (0.07,4.32)	0.44 (0.09,2.14)	0.32 (0.09,1.15)
3.26 (0.22,49.26)	1.58 (0.27,9.14)	1.06 (0.24,4.77)	1.06 (0.38,2.94)	VPZ-T7	1.01 (0.36,2.79)	0.95 (0.22,4.07)	0.89 (0.17,4.69)	0.73 (0.27,2.02)	0.59 (0.10,3.49)	0.46 (0.14,1.56)	0.34 (0.16,0.73)
3.23 (0.18,58.72)	1.56 (0.21,11.91)	1.05 (0.17,6.46)	1.05 (0.39,2.80)	0.99 (0.36,2.74)	H-VPZ-D7	0.94 (0.16,5.56)	0.88 (0.13,6.20)	0.73 (0.17,3.05)	0.58 (0.07,4.53)	0.46 (0.09,2.24)	0.34 (0.10,1.20)
3.43 (0.31,38.21)	1.66 (0.48,5.76)	1.12 (0.46,2.71)	1.11 (0.19,6.58)	1.05 (0.25,4.50)	1.06 (0.18,6.26)	H-VPZ-D14	0.94 (0.32,2.78)	0.77 (0.13,4.54)	0.62 (0.18,2.10)	0.49 (0.21,1.13)	0.36 (0.07,1.85)
3.66 (0.41,32.41)	1.77 (0.74,4.22)	1.19 (0.53,2.65)	1.19 (0.17,8.33)	1.12 (0.21,5.89)	1.13 (0.16,7.92)	1.07 (0.36,3.16)	PPI-Q14	0.82 (0.12,5.74)	0.66 (0.20,2.19)	0.52 (0.17,1.58)	0.38 (0.06,2.39)
4.45 (0.25,80.59)	2.15 (0.28,16.33)	1.45 (0.24,8.85)	1.44 (0.34,6.07)	1.36 (0.50,3.75)	1.38 (0.33,5.77)	1.30 (0.22,7.63)	1.22 (0.17,8.50)	L-VPZ-D7	0.80 (0.10,6.21)	0.63 (0.13,3.07)	0.47 (0.13,1.65)
5.57 (0.47,65.79)	2.69 (0.68,10.60)	1.81 (0.61,5.43)	1.81 (0.23,14.13)	1.71 (0.29,10.18)	1.72 (0.22,13.44)	1.62 (0.48,5.55)	1.52 (0.46,5.09)	1.25 (0.16,9.75)	VPZ-D14	0.79 (0.22,2.89)	0.59 (0.08,4.08)
7.03 (0.63,78.79)	3.40 (0.98,11.84)	2.29 (0.98,5.33)	2.28 (0.47,11.15)	2.16 (0.64,7.26)	2.17 (0.45,10.60)	2.05 (0.89,4.74)	1.92 (0.63,5.83)	1.58 (0.33,7.68)	1.26 (0.35,4.60)	PPI-T14	0.74 (0.18,3.09)
9.51 (0.57,159.62)	4.60 (0.68,31.25)	3.10 (0.57,16.71)	3.09 (0.87,10.95)	2.91 (1.38,6.17)	2.94 (0.83,10.41)	2.77 (0.54,14.22)	2.60 (0.42,16.17)	2.14 (0.61,7.54)	1.71 (0.24,11.90)	1.35 (0.32,5.66)	PPI-T7

[a] L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days

Table 7 MD and 95% CI values of VPZ- and PPI-based treatments in PP analysis[a]

Intervention	MD	95% CI
VPZ-Q14	3.40	(0.98, 11.84)
VPZ-Q10	7.03	(0.63, 78.79)
VPZ-T14	2.29	(0.98, 5.33)
VPZ-D14	1.71	(0.24, 11.90)
H-VPZ-D14	2.05	(0.89, 4.74)
H-VPZ-D7	2.17	(0.45, 10.60)
PPI-Q14	2.60	(0.42, 16.17)
VPZ-T7	2.91	(1.38, 6.17)
VPZ-D7	3.09	(0.87, 10.95)
PPI-T14	1.35	(0.32, 5.66)
L-VPZ-D7	2.14	(0.61, 7.54)
PPI-T7	0.34	(0.16, 0.73)

[a] L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days

was also to evaluate the efficacy and safety of VPZ-based and PPI-based therapies for *H. pylori* infection [58]. But it only evaluated the therapies of vonoprazan-amoxicillin (VA), vonoprazan-amoxicillin-clarithromycin (VAC), and vonoprazan-based bismuth-containing quadruple therapy (VBQT). Our work evaluated more therapies including VA, VAC, VA-bismuth, VA-sitafloxacin, VA-metronidazole, VAC-bismuth, VA-furazolidone-bismuth, VA-berberine, VA-Jing hua Wei kang capsule, conducting a thorough examination and ranking the effectiveness of these treatment regimens based on NMA results.

Limitations of the study include: (1) Despite exhaustive efforts to include all RCTs based on VPZ therapy, the sample size of the literature remains insufficient, limiting direct comparative evidence for some intervention measures. Further expansion of relevant research is necessary. (2) The focus of relevant reports primarily centers on the Asian region, potentially limiting the generalizability of findings to other populations. (3) Our study primarily investigates first-line solutions for *H. pylori* eradication, neglecting exploration

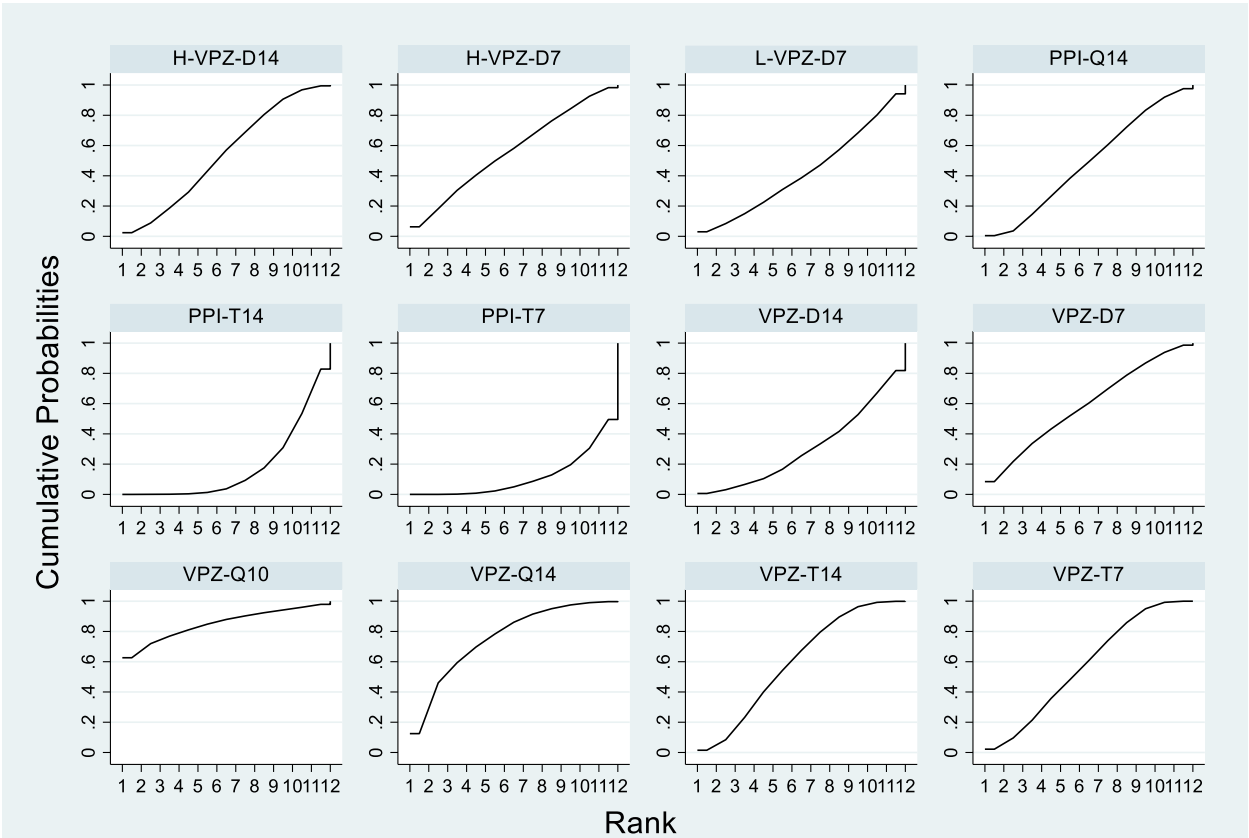

Fig. 6 SUCRA plots for eradication rate of VPZ- and PPI-based treatments in PP analysis (L: low-dose, H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 7: 7 days, 10: 10 days, 14: 14 days)

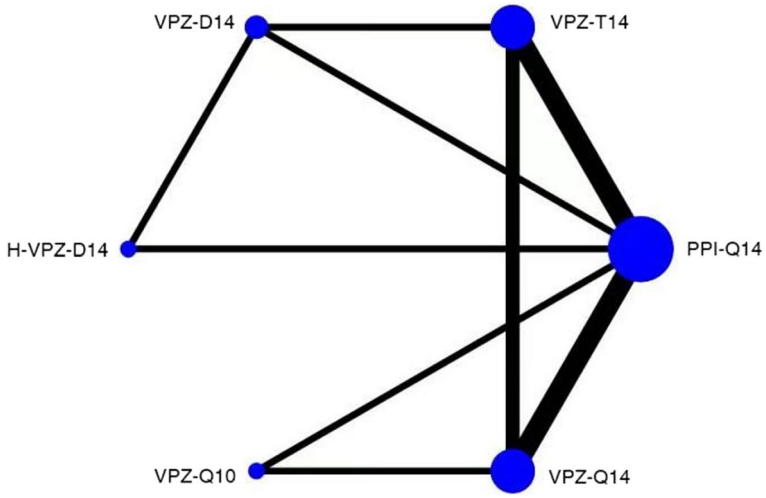

Fig. 7 The incidence of adverse effects of VPZ- and PPI-based treatments (H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 10: 10 days, 14: 14 days)

Table 8 VPZ- and PPI-based treatments for incidence of adverse effects with mean difference (MD) and 95% confidence interval (CI) values[a].

H-VPZ-D14	VPZ-T14	VPZ-D14	VPZ-Q14	PPI-Q14	VPZ-Q10
H-VPZ-D14	5.57 (0.36,86.55)	4.89 (0.54,43.94)	13.44 (0.78,232.58)	21.69 (1.63,288.54)	48.10 (1.59,1452.28)
0.18 (0.01,2.79)	VPZ-T14	0.88 (0.09,8.69)	2.41 (0.47,12.29)	3.90 (0.84,18.03)	8.64 (0.64,115.77)
0.20 (0.02,1.84)	1.14 (0.12,11.25)	VPZ-D14	2.75 (0.25,29.94)	4.43 (0.58,33.99)	9.83 (0.48,201.35)
0.07 (0.00,1.29)	0.41 (0.08,2.11)	0.36 (0.03,3.97)	VPZ-Q14	1.61 (0.39,6.67)	3.58 (0.36,35.99)
0.05 (0.00,0.61)	0.26 (0.06,1.19)	0.23 (0.03,1.73)	0.62 (0.15,2.56)	PPI-Q14	2.22 (0.23,21.59)
0.02 (0.00,0.63)	0.12 (0.01,1.55)	0.10 (0.00,2.08)	0.28 (0.03,2.81)	0.45 (0.05,4.39)	VPZ-Q10

[a] H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 10: 10 days, 14: 14 days

of second- and third-line therapies, as well as issues of reinfection and recurrence post-eradication. (4) Although this article does not impose restrictions on the combination of different antibiotics, all therapeutic antibiotics are AMO-based, with or without the addition of another antibiotic. Hence, in regions necessitating a second antibiotic, actual selection should consider local antibiotic resistance patterns.

Caution should be exercised when interpreting the results. When considering the conclusions of this study, it is essential to account for the current levels of antibiotic resistance, socio-economic development, and characteristics of the infected population in the local area.

Conclusions

Through comparing multiple intervention measures, we have reached the following conclusion: VPZ-based treatment is significantly more effective than PPI-based treatment. VPZ may emerge as the preferred medication for eradicating *H. pylori* infection. The quadruple therapy based on VPZ for 14 or 10 days exhibits the highest efficacy in terms of eradication rate and demonstrates an acceptable incidence of adverse reactions. However, currently, VPZ is recommended over PPI as the preferred intervention drug for eradicating *H. pylori* infection in patients seeking eradication. The quadruple therapy involving VPZ with treatment durations of 14 or 10 days stands as the foremost recommended

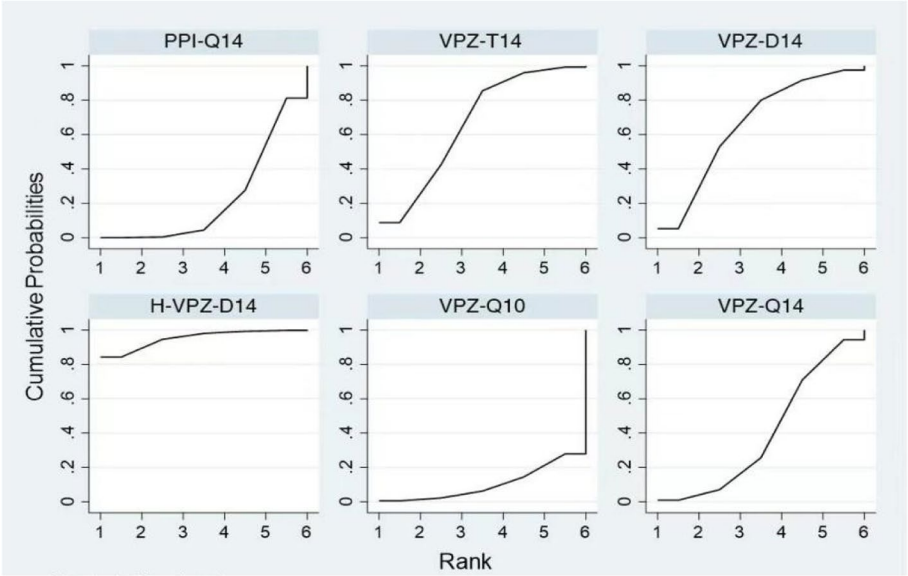

Fig. 8 SUCRA plot for the incidence of adverse effects (H: high-dose, D: dual therapy, T: triple therapy, Q: quadruple therapy, 10: 10 days, 14: 14 days)

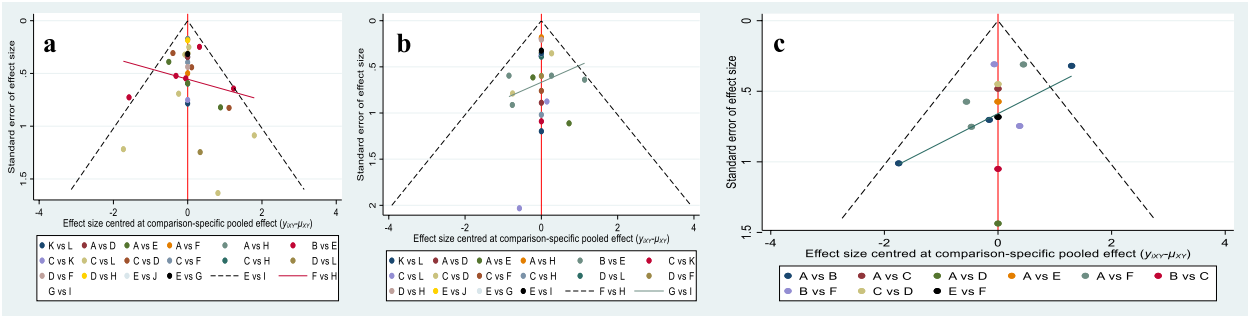

Fig. 9 Funnel plot on publication bias for (**a**) eradication rate in ITT analysis, (**b**) eradication rate in PP analysis and (**c**) incidence of adverse effects (A: H-VPZ-D14; B: H-VPZ-D7; C: L-VPZ-D7; D: PPI-Q14; E: PPI-T14; F: PPI-T7; G: VPZ-D14; H: VPZ-D7; I: VPZ-Q10; J: VPZ-Q14; K: VPZ-T14; L: VPZ- T7)

first-line intervention. In regions exhibiting high antibiotic resistance rates, a 14-day quadruple therapy incorporating VPZ bismuth is more advisable. When feasible, drug resistance testing should precede the selection of an eradication plan, facilitating the development of personalized treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09885-x.

Supplementary Material 1.

Authors' contributions

Shan Huang: investigation, visualization, and writing – original draft. Bo Li: data analysis. Xue-Yao Pang: data analysis. Wei-Wei Gao: supervision and project administration. All authors contributed to the design, interpretation of results, and critical revision of the article for intellectually important content. Shan Huang had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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